REMARKS/ARGUMENTS

Claims 22 and 24 are pending.

Favorable reconsideration is respectfully requested in view of the following remarks.

Rejection under 35 USC 112 first paragraph:

Claim 24 stands rejected under 35 USC 112 first paragraph as allegedly containing new matter. This rejection is respectfully traversed. In the amendment filed 7/11/2005 the claim 24 was amended to recite the limitation wherein "(c) sequencing the cloned Gc1 peptide, thereby confirming that the cloned Gc1 protein is a cloned wild type Gc1 protein". The Examiner argues that the original specification does not describe or suggest the concept of the sequencing procedure in step (c).

However, the Specification as filed discloses that the Applicant was able to determine, using chemically and proteolytically fragmented Gc, that the smallest domain, domain III contains an essential peptide for macrophage activation (page 10, lines 5-7). Furthermore, the Haddad reference cited in the paragraph (Haddad et al. 1992) teaches that it was known in the art to sequence peptides. This has been incorporated by reference (see page 28, lines 1-2). The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. MPEP 2163.07(b). Therefore, since this subject matter has been incorporated by reference, and should be treated as if part of the application as filed, the limitation in claim 24 is not new matter.

Accordingly, reconsideration and withdrawal of the rejection of claim 24 under 35 USC 112 first paragraph is respectfully requested.

Rejections under 35 USC 103(a)

Claim 22 stands rejected under 35 USC 103(a) as being unpatentable over U.S. Patent No. 5, 177,002 in view of Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 and U.S. Patent No. 5,516,657, Luckow (1995). This rejection is respectfully traversed.

The rejection set forth that the '002 patent discloses methods of converting Gc1 protein into GcMAF by contacting the Gc protein with β-GAL and sialidase. The Examiner admits that

the '002 patent does not disclose methods wherein the Gc protein is obtained via recombinant DNA technology and its conversion to GcMAF, but alleges that the Quirk reference sets forth the problem that viral contamination of blood products can be avoided by using recombinant DNA technology. The Examiner then relies on the Cooke reference to allegedly teach that the Gc1 allele can be cloned. The Examiner then relies on the '352 patent to disclose that human afamin, an albumin like protein can be expressed in insect cells, and that Murphy teaches baculovirus vectors, and that these vectors can be used to encode human blood factors. The Examiner finally relies on Luckow to teach that proteins expressed in the baculovirus system are antigenically, immunogenically, and functionally similar to their authentic counterparts. The Examiner finds the motivation to combine these references in that concern about viral contamination in products purified from blood may be avoided by use of recombinant DNA technology, and that the use of the baculovirus system has advantages over the use of E. coli as an expression system. The Examiner specifically recites that baculovirus has become widely used to direct the expression of foreign genes, that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells, and that expression of foreign genes in insect cells is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems.

However, "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. MPEP 2143.01.

In the Final Office Action the Examiner admits that the motivation did not come from the prior art references (Final Office Action at 3), thus the motivation must come from the nature of the problem to be solved and the knowledge of persons of ordinary skill in the art.

Here, the Examiner argues that the motivation comes from concern about human viral contamination if Gc is purified from human blood, and that these contaminants may be avoided if these products are obtained via recombinant DNA technology. The Examiner finds further

motivation in the alleged advantages of the baculovirus expression system. However, while the baculovirus expression vector system (BEVS) is one of the major recombinant DNA expression systems used today for the production of a wide variety of heterologous proteins, the Ailor reference teaches that a large fraction of the recombinant protein produced in insect cells using BEVS, can sometimes be poorly processed and accumulate as aggregates (see Ailor at 142 column 1, first paragraph). In addition, although post-translational processing in insect cells is more similar to mammalian cells than bacteria and yeast, it is not always identical and, for applications such as therapeutic proteins, this may be critical. Improper secretory processing can be especially problematic at several days post-infection when the host cell's post-translational processing machinery has deteriorated (see Ailor at 142, column 1, first paragraph). Many secreted and membrane proteins produced in insect cells, however, frequently form insoluble aggregates or are improperly processed (Ailor at 144, second column, first paragraph). Therefore the Ailor reference teaches that protein produced in the baculovirus expression system can be poorly processed and produced as aggregates, and is prone to improper post-translational modifications.

In addition, the Ho reference teaches that while BEVSs generally perform post-translational protein modifications similar to those of mammalian cells, leading to correct secretion and subunit assembly, some recombinant proteins are extensively degraded (Ho at 695, column 1, first paragraph). In addition, Ho further teaches that cells infected with baculovirus are eventually disrupted at the late stage of viral infection, leading to the loss of cellular homoeostasis and the release of proteases in conventional BEVSs, cell lysis may leak significant amounts of the engineered proteins into the medium, which are difficult to recover. In order to overcome protein degradation in BEVSs, efforts have been made to inhibit protease activity, including addition of inhibitor cocktails to the culture medium and elimination of viral protease from the viral genome. However, protease inhibitors may impair cell growth when included in culture medium, and they are expensive, particularly in large-scale expression systems. Moreover, the vulnerabilities of engineered proteins to proteolytic degradation differ, and the proteolytic activities in different insect cell lines differ as well. The optimal conditions for each case require careful and time-consuming determination (Ho at 695, paragraph bridging

paragraphs 1 and 2). Therefore, given the art recognized difficulties with the baculovirus expression systems, particularly in the production of secreted proteins, and post-translationally modified proteins, a person of ordinary skill in the art would not have been motivated to practice a method of converting Gc1 protein into GcMAF by contacting the Gc protein with β-GAL and sialidase, wherein the protein had been produced in a baculovirus system.

In addition, while obviousness does not require absolute predictability; however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976), see also Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success.). Here, while the Examiner alleges the advantages of the baculovirus expression system, the Ho reference and the Ailor references teach that there are distinct disadvantages to using the baculovirus expression system, particularly in the case of a secreted protein, which Gc1 is, wherein the baculovirus system is prone to misprocessing of secreted proteins. Additionally, in the case of post-translationally modified proteins, as Gc is, the baculovirus system degrades several days after infection, and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates. The references teach that the optimal conditions for expression of a protein in the baculovirus expression system require careful and time-consuming determination. Thus, given the teachings of the references that the baculovirus system is prone to misprocessing of secreted proteins and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates, it would not have obvious to one of skill in the art the time the invention was made to practice a method of cloning a Gc1 isoform into a baculovirus vector because there was not a reasonable expectation of success.

Accordingly, reconsideration and withdrawal of the rejection of claim 22 under 35 USC 103(a) is respectfully requested.

Claims 22 and 24 stand rejected under 35 USC 103(a) as being unpatentable over U.S. Patent No. 5, 177,002 in view of Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 and U.S. Patent No. 5,516,657, Luckow (1995), and further in view of Lu (1993). This rejection is respectfully traversed.

The rejection set forth that it would have been obvious to one of ordinary skill in the art at the time the invention was made to clone a Gc1 isoform into a baculovirus, express the cloned Gc1 isoform, contact the expressed Gc1 isoform with immobilized B-GAL and sialidase and obtain the GcMAFc as allegedly taught by the '002 patent in view of Cooke, Quirk, the '352 patent, the '657 patent, and Luckow (*supra*). The Examiner further alleges that one of ordinary skill in the art would be motivated to take the additional step of sequencing the cloned Gc1 peptide, to ensure the quality of the final GcMAFc product.

However, as above, while the Examiner alleges the advantages of the baculovirus expression system, the Ho reference and the Ailor references teach that there are distinct disadvantages to using the baculovirus expression system, particularly in the case of a secreted protein, which Gc1 is, wherein the baculovirus system is prone to misprocessing of secreted proteins. Additionally, in the case of post-translationally modified proteins, which Gc1 is, the baculovirus system degrades several days after infection, and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates. The references teach that the optimal conditions for expression of a protein in the baculovirus expression system require careful and time-consuming determination. Thus, given the teachings of the references that the baculovirus system is prone to misprocessing of secreted proteins and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates, it would not have obvious to one of skill in the art the time the invention was made to practice a method of cloning a Gc1 isoform into a baculovirus vector because there was no motivation to combine the references, and there was not a reasonable expectation of success. In addition, the Examiner has further cited the Lu reference. The Lu reference teaches that mistranslation may happen in the production of any recombinant protein, thus this reference weighs against the finding of obviousness. The Lu reference teaches that sequence error at the translational level occurs at a higher frequency (Lu at 471, column 2, first full paragraph) in bacterial expression systems.

While the Lu reference teaches bacterial expression systems, the Examiner has cited the reference to stand for the proposition that recombinantly produced proteins should be tested by sequencing after production. This is yet another reason why one of ordinary skill in the art would not have been motivated to practice the claimed method at the time the invention was made, because of the inherent problems with recombinant production of proteins. This is particularly an issue with proteins, as in the protein produced in the instant invention, wherein the proper amino acid sequence, and post-translational modifications are critical.

Lu teaches that in order to insure high product quality and to evaluate the effectiveness of manufacturing process in removing contaminants and impurities, a series of analytical methods is required to carry out extensive biochemical characterizations and biological analyses of the final purified product (Lu at 465, column 2, first paragraph). Thus, given the teachings of the Ailor and Ho references that the baculovirus system is prone to misprocessing of secreted proteins and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates, and the further teachings of Lu, as cited by the Examiner, that production of proteins by recombinant DNA technology can lead to sequence errors at the translational level, and require a series of analytical methods to carry out extensive biochemical characterizations and biological analyses of the final purified product, the claims are patentable because there is not a motivation to combine the references, and further, there was not a reasonable expectation of success.

Accordingly, reconsideration and withdrawal of the rejection of claims 22 and 24 under 35 USC 103(a) is respectfully requested.

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the

application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

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By_____

Robert S. Silver, Esq.
Registration No. 35,681
Dr. Joseph Murphy
Customer No. 03000
(215) 567-2010
Attorneys for Applicant